American Journal of Hematology 51:26–31 (1996)

Selective Discharge of Patients With Acute Myeloid Leukemia During Chemotherapy-Induced Neutropenia

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Purpose. It is common practice for patients with acute myeloid leukemia (AML) to be observed in hospital during the entire nadir after intensive chemotherapy. In an attempt to lessen the likelihood of developing infections with hospital acquired pathogens, we usually discharge patients upon completion of chemotherapy and follow them as outpatients. They are readmitted if fever develops. We evaluated the feasibility and safety of this practice.

Patients and Methods. We studied 29 patients with AML (median age 40 years, range 16–63) who were treated with intensive remission-induction and consolidation chemotherapy. Afebrile patients not receiving antibiotics were discharged immediately following chemotherapy and were followed every 3–4 days at the day care unit. Patients were instructed to return immediately if fever rose to 38.2°C or a fever of 38°C persisted for 2 hr. The 29 patients received a total of 86 courses. Following 50 courses, patients were discharged. These 50 ambulatory nadir periods (ANPs) were monitored.

Results. Median WBC and platelet counts on discharge were 2,900 per cubic millimeter (range 300–8,300) and 137,000 per cubic millimeter (range 17,000–618,000), respectively. Mean traveling time from the hospital by car was 1.6 hr (range 15 min–3 hr). In three of the 50 ANPs (6%), patients were not readmitted during their entire nadir. During 47 of the ANPs, patients returned to the hospital (because of fever in 44 cases), a mean of 7.2 days (range 1.0–12.7 days) after discharge. In 45 ANPs, patients were readmitted in good general condition. Four patients had life-threatening complications. Two patients were admitted in septic shock due to delay in seeking admission, but rapidly recovered. Two other patients died, one of cardiogenic shock within 24 hr of readmission and one 24 days later. Only one of the 11 gram negative bacteria cultured was resistant to mezlocillin and gentamicin. After 45 ANPs, patients were discharged a mean of 12.2 days (range 5–42 days) following readmission. We estimate that approximately 383 hospital days were saved by this policy, a mean of 7.6 days per patient, representing 16% of total inpatient hospital days.

Conclusions. For AML patients who are reliable and without complicating medical conditions, selected discharge following chemotherapy is a low-risk practice and may reduce the incidence of infection with resistant hospital-acquired pathogens.

Key words: leukemia, neutropenia, ambulatory medicine

INTRODUCTION

Infections are a major cause of morbidity and mortality during the period of granulocytopenia following chemotherapy [1–2]. Patients with acute myeloid leukemia (AML) are especially susceptible to bacterial infections due to the intensive chemotherapy administered during remission induction and consolidation treatment [3]. It is well established that it is imperative to immediately administer empiric, broad-spectrum antibiotic treatment to the febrile granulocytopenic host [1–2]. However, the optimal way to monitor the afebrile granulocytopenic patient has not been agreed upon. Traditionally these patients have been observed as inpatients. In some studies examining the value of antibiotic prophylaxis in afebrile

Received for publication March 31, 1995; accepted August 9, 1995.

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granulocytopenic patients, patients were observed in single rooms with [4] or without positive laminar airflow [3,5–8], or on an open ward [3,6,9]. In another study, patients stayed at a nearby hotel and were examined daily [10]. In other studies, some patients were treated as outpatients although details are not given [9,11].

Anecdotal reports suggest that outpatient management of afebrile neutropenic patients is becoming acceptable clinical practice in the United States. However, this practice has not been systematically studied as to its safety and cost effectiveness.

At Hadassah Medical Center, we usually discharge AML patients regardless of their blood counts as soon as chemotherapy administration ends, if they are afebrile and are not receiving antibiotics. This is based on the assumption that infections acquired outside the hospital are more likely to be caused by less virulent pathogens than nosocomial infections. Patients return home, even though some live a considerable distance from the hospital, and are followed on an ambulatory basis every 3–4 days. They are readmitted if fever or other serious complications develop.

We prospectively evaluated this practice over an 18 month period. In particular, we examined the probability of discharge after chemotherapy administration ends, the length of time spent at home before fever developed, and the incidence and type of organisms which accounted for infectious readmissions. The major endpoints used in determining the safety of this policy were the rates of complication including morbidity and mortality. The number of hospital days saved by selective discharge of these patients was estimated using this data.

PATIENTS AND METHODS

All adult patients with de novo or secondary AML, either newly diagnosed or in relapse, who were admitted to our hospital between February 1, 1992 and August 1, 1993 and were treated with intensive chemotherapy, are included in this study. During the study period, 29 patients were observed, 24 with de novo AML and five with secondary AML. Five patients had relapsed disease including three whose induction treatment had been given earlier in the study period. Their median age was 40 years (range 16 to 63). Each patient received a mean of 2.9 courses of chemotherapy (range 1 to 6), for a total of 86 courses administered during the study period.

Induction chemotherapy consisted of daunorubicin (45 mg/m^2 daily for 3 days; over age 60 reduced to 30 mg/m^2 daily for 3 days) and cytosine arabinoside (100 mg/m^2/day by continuous infusion for 7 days). This was followed by consolidation with high dose cytosine arabinoside (1–3 g/m^2, twice daily for 5–6 days) and an additional cycle consisting of etoposide (100 mg/m^2, days 1–5) and mitoxantrone (12 mg/m^2, days 1–3).

Patients who relapsed were treated either with one of the above protocols or with high dose cytosine arabinoside (3 grams/m^2 daily for 5 days) and high dose mitoxantrone (20 mg/m^2, days 1–2). Hickman catheters were usually inserted only if difficulty existed in obtaining peripheral venous access.

Patients were discharged at the termination of chemotherapy administration, regardless of their white blood cell (WBC) count or platelet counts, if they were in good general condition (i.e., fully ambulatory) had no obvious source of infection, were afebrile and were not receiving antibiotics.

Patients living near the hospital were examined at the day care clinic every 3–4 days and received blood products as necessary. Those living at a greater distance were usually examined 1 week after discharge and then twice weekly.

Patients were instructed in general and oral hygiene and antiseptic mouthwashes were recommended. Prophylactic oral antibiotics were not prescribed. Cytokines (granulocyte or granulocyte-monocyte colony stimulating factor) were not administered to any patient. We instructed patients to measure their oral temperature twice daily and to return immediately to the hospital if their temperature rose to 38.2°C or more, or if a fever of 38°C persisted for 2 hr. They were also instructed to return if rigors, local signs of infection, a bleeding tendency, or any other complication developed.

Patients were encouraged to call if questions arose and advice was available via telephone 24 hr a day from the hematology fellow on call and the hematology department nurses. As a result, we were notified by most patients of their imminent return to the hospital. Therefore, upon arrival, the patient could be seen by the hematology fellow or physician on call without delay. Cultures (blood, urine, and when relevant, throat, sputum, and stool) were urgently obtained and an effort was made to start broad-spectrum antibiotics within 30 min of arrival at the emergency room. Complete blood counts were performed on a Coulter S-Plus IV (Coulter Electronics Limited, Luton, UK) and peripheral blood smears were examined by one of the authors to confirm the granulocyte count. Initial antibiotic therapy consisted of gentamicin, mezlocillin, and cefazolin. Changes in antibiotics and the addition of amphotericin were made according to the guidelines of the Working Committee of the Infectious Diseases Society of America [2].

RESULTS

Twenty-two patients treated for AML during the study period were discharged and followed on an ambulatory basis at the end of 50 of the chemotherapy courses. We concentrated our analysis on these 50 ambulatory nadir periods (ANPs). Seven patients observed during the study

TABLE I. Likelihood of Discharge Relative to the Type of Chemotherapy Course Given

No. courses		Discharge possible (%)	Discharge not possible (%)
Induction	33	4 (12)*	29 (88)
Consolidation	53	46 (87)*	7 (13)
Total	86	50 (58)	36 (32)

*$P < 0.001$

period were never able to be discharged after any course of therapy. Overall, it was frequently possible to discharge the patients following chemotherapy (Table I). Furthermore, significantly more patients (46 vs. 4, $P < 0.001$) were discharged after cycles of consolidation chemotherapy than after remission induction therapy (Table I). This was because many of the induction courses were administered to patients who were initially febrile or who developed fever during these courses. On the other hand, only rarely did patients start consolidation treatment while receiving antibiotics. Fever developed rarely while consolidation chemotherapy was being administered.

There were 36 additional chemotherapy courses administered during the study period following which discharge was not possible due to: fever treated with antibiotics (34 courses), early death (1 course), and social reasons (1 course). Seven patients (11 courses) were never discharged after any of their cycles of chemotherapy.

These seven patients who were never discharged (of whom 2 had secondary leukemia) were on average older than the 22 patients who were discharged at least once (49 years vs. 36 years, $P = 0.04$) and had a much poorer outcome (3 died during remission induction and only 3 entered a complete remission).

Mean travel time from hospital by car was 1.6 hr (range 15 min to 3 hr). Eleven patients resided more than 2 hr travelling time from the hospital. Median WBC and platelet counts on discharge were 2,900 per cubic millimeter (range 300 to 8,300) and 137,000 per cubic millimeter (range 17,000 to 618,000), respectively. In six cases, patients were discharged with an absolute neutrophil count of less than 500 per cubic millimeter.

During the 50 ANPs, patients were seen at the day care unit a mean of 0.94 times (range 0–4). During 19 ANPs, patients were not seen even once, in most cases due to early readmission. Blood transfusions were administered at the day care unit in 15 of the ANPs and platelet concentrates in 10. During 19 ANPs, 10 patients had indwelling Hickman catheters which were routinely flushed in the day care unit. In three of the 50 ANPs (6%), patients were not readmitted during their entire nadir.

During 47 of the ANPs, patients returned to the hospital because of fever (44 cases) or other complications (bleeding, cytosine arabinoside-induced keratitis, and sore throat without fever) in three cases. Mean time out of hospital, calculated to the nearest hour, was 7.2 days (range 1.0 to 12.7 days). As expected, the 10 patients discharged with a WBC count of 1,500 per cubic millimeter or less returned earlier than the 37 patients discharged with a higher WBC (3.2 days vs. 8.2 days, $P = 0.0001$). The three patients who did not return during the entire nadir all had a WBC of more than 2,900 per cubic millimeter on discharge.

During 47 ANPs, patients required readmission. Of these, in 45 instances, patients were in good general condition on admission. Two patients, who delayed their readmission by at least 24 hr after onset of fever, were brought in septic shock (anuria, systolic blood pressure <80 mmHg) but rapidly recovered. One of these patients had been initially admitted to a local hospital where he was inadequately treated for pseudomonas sepsis.

Out of 45 ANPs during which patients were readmitted in stable condition, two deaths occurred. One patient, aged 60, abruptly deteriorated 8 hr following readmission and died within 24 hr from cardiogenic shock and *E. coli* bacteremia (sensitive to the antibiotics she received).

The second fatality occurred in a patient with resistant relapsed disease, who died 24 days after readmission because of prolonged bone marrow aplasia, disseminated fungal infection, and multiorgan failure.

Mean WBC count on readmission was 549 per cubic millimeter (range 100–2,000). In 40 instances, patients were readmitted with 0–100 granulocytes per cubic millimeter and 7 with 100–500 granulocytes per cubic millimeter.

Mean platelet count on readmission was 21,000 per cubic millimeter (range 1,000 to 191,000). In 22 cases, the platelet count was less than 10,000 per cubic millimeter. Only one patient returned because of a bleeding tendency. Mean hemoglobin on readmission was 8.7 g per deciliter (range 5.3–12.1).

In 17 out of the 47 ANPs studied (36%) blood cultures were positive on admission. In Table II, the type of bacteria isolated, the number of antibiotic resistant strains, and the source of the positive blood cultures are detailed. In four cases, polymicrobial bacteremia was documented. Ten of the 11 gram negative bacteria were sensitive to at least two of the three drugs of our first-line antibiotic protocol (cefazolin, mezlocillin, and gentamicin). The single exception was a patient with *E. coli* bacteremia. However, this patient had been treated in hospital 2 weeks previously for a urinary tract infection caused by a resistant *E. coli* and his initial antibiotic therapy had been modified accordingly. Three of the six *Staphylococcus* coagulase negative were methicillin resistant. All of these were identified in patients who had Hickman catheters and the bacteria were isolated only in cultures from the Hickman and not from peripheral blood cultures taken

TABLE II. Bacterial Isolates From Blood Cultures of 17 Febrile Patients on Readmission: Total Number (Number of Drug Resistant Strains)

Bacteria	No. of isolates	Source: Peripheral blood	Source: Hickman
Escherichia coli	7 (1)	5 (0)	2 (1)
Staphylococcus coagulase negative	6 (3)		6 (3)
Staphylococcus coagulase positive	3 (0)	2 (0)	1 (0)
Pseudomonas aeruginosa	1 (0)	1 (0)	
Enterobacter cloacae	1 (0)		1 (0)
Proteus mirabilis	1 (0)		1 (0)
Klebsiella pneumoniae	1 (0)		1 (0)
Streptococcus viridans	1 (0)[a]	1 (0)	1 (0)
Total	21 (4)[b]	9 (0)	13 (4)

[a]Same bacteria isolated simultaneously from Hickman catheter and peripheral blood cultures.
[b]Four patients had polymicrobial bacteremia.

simultaneously. All three *Staphylococcus* coagulase positive isolates were sensitive to cefazolin.

In 45 ANPs, patients were discharged from hospital a mean of 12.2 days (range 5–42 days) following readmission. In 36 ANPs, patients were discharged within 48 hours of their absolute neutrophil count rising to 500 per cubic milliliter. In 9 cases, hospitalisation was required for an additional period of 11.9 ± 9.5 (median 7) days following recovery of their neutrophil count. Only three of these patients were hospitalised for more than 10 days, because of probable *Pneumocystis carinii* pneumonia, a leg abscess requiring open surgical drainage, and an overwhelming hospital-acquired pseudomonas infection requiring prolonged mechanical ventilation (one case each).

DISCUSSION

The optimal management of the afebrile granulocytopenic patient is still controversial. In the past, strict isolation in rooms with laminar air flow was advocated [12], however this policy has not definitively been shown to reduce or delay febrile episodes [13]. In many medical centers, AML patients are observed in hospital during their entire period of nadir [3–8,14–16]. An important consideration in not discharging patients is the need for close observation and for immediate antibiotic therapy if fever develops. Although anecdotal reports suggest that outpatient management of afebrile neutropenic patients is becoming acceptable practice in the United States, its safety has not been systematically studied. Although the best means to evaluate this practice would be a prospective, randomized study, we undertook a nonrandomized but systematic prospective observation period to define the possible risks and benefits.

In our center we discharged patients following the majority (58%) of chemotherapy courses administered. However, when broken down by the type (induction vs. consolidation), discharge was only feasible following 87% of consolidation courses. The failure to discharge patients following induction was due to the fact that half of the newly diagnosed AML patients (and patients in relapse) presented with fever and neutropenia which required empirical antibiotic treatment.

Our practice of discharging afebrile patients following chemotherapy is based on several assumptions. First, there may be less risk of infection with hospital-acquired pathogens if the period of hospitalisation is shortened. Second, patients can be trained to reliably note early onset of symptoms which require treatment. Furthermore, a delay of several hours in starting antibiotics once fever develops may not adversely affect the patient's outcome, if patients seek hospitalisation immediately upon becoming symptomatic. Lastly, ambulatory instead of inpatient observation is likely to reduce the overall cost of the AML patient care. Our findings support these assumptions.

First, the overall percent of positive blood cultures (36%) is similar to that (32%–35%) in a published series [17] indicating that the slight delay in starting antibiotic therapy (due to travel and time required for readmission) did not result in an increased number of documented bacteremic episodes. Furthermore, in 10 out of 11 cases of gram negative bacteremia, the bacteria were sensitive to at least two of the three antibiotics we have used as our first line protocol for the last 15 years. The single exception was a patient with a documented urinary tract infection with the same organism two weeks previously during a prolonged hospitalisation. This contrasts with the high incidence of colonisation and infection with resistant gram negative bacteria associated with prolonged hospitalisations [18]. It is not possible to directly compare the infectious complications of patients who were discharged with those who were not, because most of the latter were admitted with fever and were treated with antibiotics during their entire hospitalisation.

Patients from varied sociological and educational backgrounds can be trained to note and act upon signs and symptoms of complications requiring immediate treatment. Many of our patients have received less than a high school level of formal education, yet all were able to comply with instructions to measure temperature twice daily, to observe for petechiae, to note rigors if they occurred, and to return immediately to the hospital if one of these events developed. Patients were cautioned as to the potentially serious consequences of delay in seeking medical attention.

In fact, the only two patients who were admitted in septic shock had been febrile for at least 24 hr and had

failed to follow instructions for immediate return to our hospital.

In one case, the patient returned to a local hospital where he was initially inadequately treated before being transferred. In the other case, the patient failed to comprehend the serious consequences of deferring treatment and thus knowingly delayed readmission. Both patients rapidly recovered without sequelae. Neither required intensive care unit admission or intubation. These two incidents underscore the importance of ensuring the patient's complete comprehension of all instructions prior to release from hospital, particularly since most patients will arrive early in the course of the infectious process before they are severely symptomatic. As in patients with sickle cell disease who are also immunocompromised, well-informed and highly motivated family members can play a vital role in the outpatient monitoring of these patients [19].

One patient died soon after readmission. This 60-year-old patient with a history of a remote myocardial infarction was asymptomatic when routinely examined by one of our own hematologists 6 hr prior to admission. Four hours later fever developed and she arrived at our hospital 2 hr later. Antibiotics were started within 20 min of admission. Eight hours later, after she had received 2 doses of antibiotics, she suddenly developed cardiogenic shock and died within 24 hr of admission.

Blood cultures grew *E. coli* sensitive to the antibiotics she received. This patient had developed transient biventricular cardiac failure during all-trans-retinoic acid administration, which improved with diuretic administration. We can not exclude the possibility that in this patient with diminished cardiac reserve, the 2 hr delay in initiating antibiotics contributed to her early death.

We attempted to estimate the number of hospital days saved by our practice of discharge following chemotherapy. For patients who were eventually readmitted, the average length of time spent at home was 7.2 days (actual total for 47 ANPs was 338 days). For three patients not admitted during an entire nadir, we estimate a minimum saving of 15 days per ANP (total was 45 days). This totals an estimated 383 hospital days which were saved over the study period. This represents a saving of 16% in the total inpatient days required to administer all 86 courses to the 29 patients.

In examining the number of hospital days saved by discharging patients following chemotherapy, we do not believe that this practice prolonged the patients' hospitalisation following readmission. The total average time from beginning chemotherapy until discharge following readmission did not exceed total duration of an inpatient course of standard chemotherapy as published in the literature.

The total duration of each of our courses was, on average, 24–26 days, consisting of chemotherapy administration (5–7 days), ANP (7.2 days), and readmission (12.2 days) which is similar to the 22–28 days reported for induction and consolidation courses in recently published series [15–16]. The median age of 39 for our patients is somewhat younger than the median age of 44–56 in other recent studies on AML patients [14–16]. We assume that the young age reflects referral bias to our tertiary care facility.

There have been many studies aimed at preventing febrile episodes in the neutropenic patient. Some centers prescribe prophylactic antibiotics based on the results of studies using either trimethoprim-sulfamiethoxazole [2–4,6–11,20–21] or norfloxacin [5,8,21–22].

We did not prescribe prophylactic antibiotics, to avoid masking partially treated bacteremia in patients who were not monitored daily. Further, we wished to avoid the selection of more virulent antibiotic-resistant strains which can result from the use of prophylactic antibiotics [23].

We conclude that for reliable compliant patients, with the exception of the elderly or those with other severe medical conditions, selected discharge of AML patients during chemotherapy induced neutropenia is generally safe. It is particularly relevant for patients undergoing consolidation chemotherapy after which discharge was possible, following 87% of courses. The potential risks must be weighed against the possible benefits, in that this practice may also reduce the incidence of infection with resistant hospital-acquired pathogens. Our practice also enabled us to make more effective use of limited hematology bed space—an important consideration in this era of limited resources. Recent reports have advocated outpatient antibiotic therapy of febrile neutropenia in cancer patients, including some with AML [24–25]. If such management were combined with our approach, many AML patients could be managed at home for a considerable proportion of their treatment. Only a prospective multicenter trial using a randomized format could provide definitive answers to the issue of safety and cost effectiveness of ambulatory post chemotherapy monitoring. Our results provide a basis for the establishment of guidelines for such a study.

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